Journal of the American College of Cardiology Vol. 60, No. 11, 2012

ISSN 0735-1097/$36.00

CORRESPONDENCE

Letters to the Editor

Osteoporosis Is a Major Confounder in Observational Studies Investigating Bisphosphonate Therapy in Aortic Stenosis

We read the paper "Do Bisphosphonates Slow the Progression of Aortic Stenosis" by Aksoy et al. (1) with great interest. Given the central role that calcification plays in the progression of aortic stenosis, the question as to whether bisphosphonates might favorably modify this disease process is an important one.

In their large retrospective study, the researchers found that there was no difference in aortic stenosis progression between women who were taking and not taking bisphosphonate therapy after a median follow-up of 1.6 years. This lack of effect persisted even after sophisticated propensity matching; however, we believe that this analysis did not correct for one potentially important confounder.

The link between osteoporosis and increased vascular calcification, the so-called calcification paradox, is well established, and the researchers themselves previously extended this principle to aortic valve calcification (2–4). We therefore believe that the presence of osteoporosis in those prescribed bisphosphonate therapy may have had a significant incremental effect on aortic stenosis progression. As such, the lack of difference between the groups could be interpreted as a sign that bisphosphonates were in fact successful in normalizing disease progression in these patients.

In our opinion, it is unlikely that observational studies will be able to disentangle the effects of bisphosphonates and osteoporosis on aortic stenosis. The true impact of these drugs will only become clear within the setting of a randomized controlled trial.

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http://dx.doi.org/10.1016/j.jacc.2012.04.048

REFERENCES

1. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? J Am Coll Cardiol 2012;59:1452–9.
2. Aksoy Y, Yagmur C, Tekin GO, et al. Aortic valve calcification: association with bone mineral density and cardiovascular risk factors. Coron Artery Dis 2005;16:379–83.
3. Persy V, D'Haese P. Vascular calcification and bone disease: the calcification paradox. Trends Mol Med 2009;15:405–16.
4. Raggi P, Giachelli C, Bellasi A. Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. Nat Clin Pract Cardiovasc Med 2007;4:26–33.

Reply

We thank the correspondents for their interesting comment on our recent paper (1). We would like to point out, however, that none of the authors of the present paper have been associated with the papers that they referenced. The calcification paradox whereby vascular calcification is more prevalent in those with reduced bone density or increased bone turnover has been well described. Increased valvular calcification has also been described in patients with osteoporosis, but specific data on whether osteoporosis accelerates aortic stenosis progression has not to our knowledge been reported. Additionally, we have no way of knowing whether the elderly women in our study who did not receive bisphosphonates had some degree of osteoporosis. The fact that many were receiving vitamin D and calcium supplementation suggests that a proportion at least were considered at risk for osteoporosis. The correspondents' contention that bisphosphonates in our study may have normalized an acceleration of aortic stenosis associated with osteoporosis is therefore interesting but still hypothetical. We agree with the correspondents and stated in our conclusions to the paper that prospective clinical trials of specific bisphosphonates will be needed to fully answer the question of the impact of this class of drugs on aortic stenosis progression.

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REFERENCE

1. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? J Am Coll Cardiol 2012;59:1452–9.

Challenging Interpretation of Elevated Cardiac Troponin T in a Complex Case With Rhabdomyolysis

We read with interest the correspondence letter by Sribhen et al. (1) referring to the article "Diseased skeletal muscle: a noncar-

diac source of increased circulating concentrations of cardiac troponin T" by Jaffe et al. (2) published in the October 2011 issue of the *Journal*. In their letter, Sribhen et al. (1) share their experience on a case of a 27-year-old man experiencing severe rhabdomyolysis after abdominal surgery due to intestinal herniation with bowel gangrene. Initially, this patient showed a concordant increase in the third-generation cardiac troponin T (cTnT) and cTnI assays on the third post-operative day with a consecutive fall in cTnT and cTnI levels. Subsequently, the cTnI level decreased to reference ranges, whereas the cTnT level began to rise again, reaching a maximum on the 18th post-operative day. Based on the report of Jaffe et al. (2), the researchers argued that these findings support the hypothesis that the re-elevation of the cTnT level might be the consequence of re-expression of cTnT isoforms in skeletal muscle during the subacute phase of rhabdomyolysis. In support of their hypothesis, the researchers argued that a higher rate of elevations in cTnT level as compared with cTnI level is also found in end-stage renal disease (3) and quoted reports on cross-reactivity of the first-generation TnT assay (4).

In our view, this interpretation is neither substantiated by their data nor the data provided by Jaffe et al. (2) in the original paper or his comments accompanying this letter.

First, extensive testing during development of the cTnT assay showed no false positive cTnT elevations, even in patients with severe skeletal muscle injury and extremely high blood creatine kinase activity.

Second, in the particular patient reported by Sribhen et al. (1), there are many possible reasons for elevations in cTnT and cTnI levels on the third post-operative day, such as post-operative myocardial infarction, acute renal failure, systemic inflammatory response syndrome due to intestinal gangrene, and pulmonary embolism, to name only a few. These established causes of troponin release are—in our opinion—a much more likely explanation for the cTnT elevations than re-expression of cTnT isoforms in skeletal muscle. There have been no scientific data yet indicating re-expression of cTnT in skeletal muscle in severely diseased patients in the intensive care setting.

Third, the reasons for the discordant findings of cTnI and cTnT are unclear, and the limited clinical information provided by Sribhen et al. (1) does not contribute to clarification. Several factors may interfere with the cTnI measurements, causing a false negative result, such as hemolysis, heparin interference, autoantibodies, heterophilic antibodies, and a lower analytical sensitivity and precision of the third-generation cTnI versus cTnT assay (5).

The observation of cTnT, and less often cTnI, elevations in some patients with skeletal muscle myopathy or dystrophy is interesting and most likely explained by myocardial involvement due to a systemic disorder. Nevertheless, the possibility of re-expression of cTnT in skeletal muscle merits thorough scientific evaluation. However, the study cohort reported by Jaffe et al. (2), which is used in support of the case, is subject to an inherent inclusion bias because only those patients who were cTnI negative but cTnT positive were included in the trial. So far, no data are available in an unselected population with skeletal muscle diseases. In their paper published in the *Journal*, Jaffe et al. (2) concluded that they found the "same molecular weight proteins in diseased skeletal muscle and in the heart." However, looking closer at the figures revealed that immunoreactive proteins in the diseased skeletal muscle detected by Western blotting had a different molecular weight as compared with cTnT in heart muscle (Fig. 2 of their article). For the soleus muscle extract, 2 peptides were heavily stained using the monoclonal cTnT antibody M7, and these peptides had molecular weights much lower than cTnT (Fig. 3 of their article). Interestingly, the skeletal muscle samples were not probed for cTnI re-expression. Thus, it is impossible to prove the re-expression of troponin T in skeletal muscle by these experiments. Only sequencing of the proteins that were stained by the antibodies in the Western blot would clarify if indeed a cTnT fragment or much more likely unspecific binding of the antibodies in tissue sections could explain the staining in the Western blot.

We believe that interpretation of elevated cTn concentrations, particularly when more sensitive assays are used, has become a challenging task for clinicians. However, the case by Sribhen et al. (1) and the explanations provided by Jaffe et al. (2) are not substantiated by robust scientific data and therefore will not aid in explaining the TnT elevations in this complex case.

There is a large database indicating that elevation of cTns in the absence of acute coronary syndrome, commonly mislabeled as a false-positive cTn result, is an independent predictor of patient outcome, particularly if myocardial damage is due to a different mechanism than myocardial ischemia. Thus, so far there are no robust scientific data supporting the hypothesis that re-expression of cTnT in skeletal muscle may be a reasonable explanation for elevated TnT levels in critical care.

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http://dx.doi.org/10.1016/j.jacc.2012.05.028

REFERENCES

1. Sribhen K, Phankingthongkum R, Wannasilp N. Skeletal muscle disease as noncardiac cause of cardiac troponin T elevation (letter). J Am Coll Cardiol 2012;59:1334–5.
2. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. J Am Coll Cardiol 2011;58:1819–24.
3. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002;106:2941–5.
4. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kübler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. J Mol Cell Cardiol 1989;21:1349–53.
5. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.

Reply

We thank Drs. Giannitis and Katus for their interest in our paper (1) concerning the clinical specificity of cardiac troponin T (cTnT)